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From: Steadman, David (AU1652)
Sent: Thursday, March 23, 2006 9:13 AM
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Subject: 10/601,011 sequence alignment request

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NAME: David Steadman

AU: 1656

Date: 3/23/06

Office: Remsen 2B05

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Please align the following sequences:

amino acids 126-388 of SEQ ID NO:1 of application 10/601,011 against SEQ ID NO:1 of application 10/979,375

Please save results to diskette.

Thank you very much.

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656
Protein Crystallography and Recombinant Enzymes
Office: Remsen 2B05
Mailbox: Remsen 3C70
Phone: (571) 272-0942

1-403 AA

Searcher: Forster
Searcher Phone: _____
Date Searcher Picked up: 2/24
Date completed: _____
Searcher Prep Time: _____
Online Time: _____

Type of Search
NA# _____ AA# 1
S/L: _____ Oligomer: _____
Encode/Transl: _____
Structure #: _____ Text: _____
Inventor: _____ Litigation: _____

Vendors and cost where applicable
STN: _____
DIALOG: _____
QUESTEL/ORBIT: _____
LEXIS/NEXIS: _____
SEQUENCE SYSTEM: _____
WWW/Internet: _____
Other (Specify): _____

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	13528	(aik or aurora)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 10:35
S2	1245	S1 and crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 09:30
S3	21	S1 near5 crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 09:30
S4	190	(aik? adj protein) or (aurora\$ adj kinase) or (aur adj kinase) or (stk15 adj kinase) or (btak adj protein)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 10:42
S5	27	S4 and (crystal or (unit adj cell))	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 13:19
S6	190	(aik? adj protein) or (aurora\$ adj kinase) or (aur adj kinase) or (stk15 adj kinase) or (btak adj protein)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 13:20
S7	0	S6 and (cronin.in. or knuth.in. or mcree.in. or nowakowski.in. or pavletich.in. or thompson.in. or wijnands.in.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 13:20
S8	2	S6 and (takeda.as. or syrxx.as.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/03/23 13:21

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 April 2003 (17.04.2003)

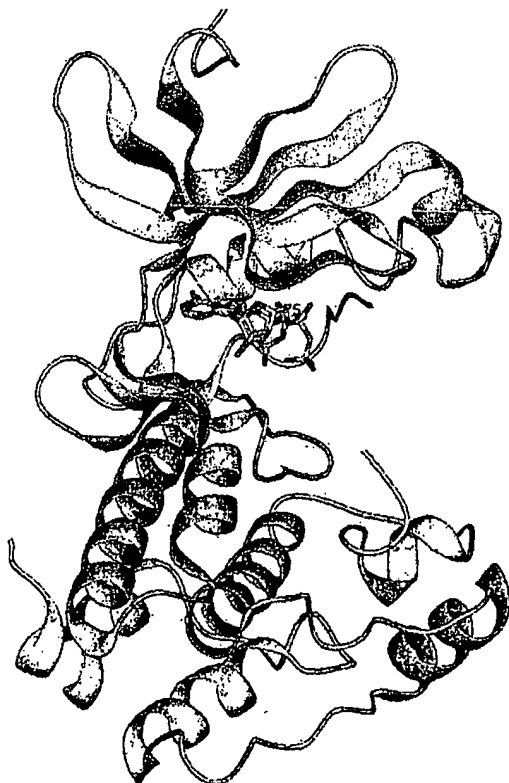
PCT

(10) International Publication Number
WO 03/031606 A3

- (51) International Patent Classification⁷: **C12N 9/12**
- (21) International Application Number: **PCT/GB02/04589**
- (22) International Filing Date: **8 October 2002 (08.10.2002)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
0124299.9 10 October 2001 (10.10.2001) **GB**
- (71) Applicant (*for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, FR, GB, GD, GE, GH, GM, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MK, MN, MW, MX, MZ, NL, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only*): **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).
- (71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1Y 6LN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **ANDERSON, Malcolm** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **KEEN, Nicholas, John** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **PANNIFER, Andrew, David, Bruce** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **PAUPTIT, Richard, Alexander** [NL/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **ROWSELL, Sian** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).
- (74) Agent: **ASTRAZENECA**; Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

[Continued on next page]

(54) Title: **CRYSTAL STRUCTURE OF AN AURORA KINASE CATALYTIC DOMAIN, AND USE THEREOF**



(57) Abstract: The invention provides crystalline forms of a polypeptide corresponding to the catalytic domain of Aurora kinase. The active site ATP binding pocket is defined by its amino acid residues and their atomic coordinates. This structure may be used to select or design chemical modulators of Aurora kinase, particularly Aurora inhibitors. These modulators may be used to treat diseases of cell proliferation, e.g. cancer.

WO 03/031606 A3

Internat	Application No
PCT/GB	02/04589

According to International Patent Classification (IPC) or to both national classification and IPC

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, MEDLINE

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>BISCHOFF JAMES R ET AL: "The Aurora/Ipl1p kinase family: Regulators of chromosome segregation and cytokinesis." TRENDS IN CELL BIOLOGY, vol. 9, no. 11, November 1999 (1999-11), pages 454-459, XP002254572 ISSN: 0962-8924 the whole document</p> <p style="text-align: center;">---</p>	<p>1-11, 13-16</p>
Y	<p>"Solutions for crystal growth" HAMPTON RESEARCH, 'Online! 15 April 2001 (2001-04-15), XP002254573 Retrieved from the Internet: <URL:http://web.archive.org/web/2001041520 5238/www.hamptonresearch.com/hrproducts/sc reens.html> 'retrieved on 2003-09-15! the whole document</p> <p style="text-align: center;">---</p>	<p>1-11, 13-16</p>

-/--

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 September 2003

Date of mailing of the International search report

30/09/2003

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer _____

Wimmer, G

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/GB 02/04589

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MUELLER U ET AL: "Development of a technology for automation and miniaturization of protein crystallization" BRAUWELT, NUERNBERG, DE, vol. 85, no. 1, 23 January 2001 (2001-01-23), pages 7-14, XP004315104 ISSN: 0168-1656 the whole document	1-11, 13-16
T	CHEETHAM GRAHAM M T ET AL: "Crystal structure of Aurora-2, an oncogenic serine/threonine kinase." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 45, 8 November 2002 (2002-11-08), pages 42419-42422, XP002254574 ISSN: 0021-9258 the whole document	1-11, 13-16
A	SARIDAKIS E ET AL: "IMPROVING PROTIEN CRYSTAL QUALITY BY DECOUPLING NUCLEATION AND GROWTH IN VAPOR DIFFUSION" PROTEIN SCIENCE, CAMBRIDGE UNIVERSITY PRESS, CAMBRIDGE, GB, vol. 9, no. 4, April 2000 (2000-04), pages 755-757, XP009010758 ISSN: 0961-8368 the whole document	1-11, 13-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/04589

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 12 relates to a method of designing a three-dimensional structure. As such a threedimensional structure is merely a form of display of information, subject-matter of the claim is regarded to fall under the provisions of Art. 52(2)d.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 3 and 4 relate to a crystalline polypeptide defined by reference to certain parameters, wherein it is impossible to compare these parameters to what is set out in the prior art. Consequently, a lack of clarity arises to such an extent as to render a meaningful complete search impossible.

Likewise, claims 5 and 16 relate to a crystalline polypeptide defined by the presence of certain parameters, namely individual residues at specific steric coordinates. A comparison of such absolute individual steric coordinates with what is set out in the prior art appears not to be possible and/or meaningful, leading to a lack of clarity to such an extent as to render a complete search impossible.

Moreover, these claims therein relate to an extremely large number of possible compounds, however support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found only for the specific Aurora A kinase peptide crystals disclosed in the application.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to a crystalline form of an Aurora kinase.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
13 November 2003 (13.11.2003)

PCT

(10) International Publication Number
WO 2003/092607 A3

(51) International Patent Classification⁷: **A61K 31/517**,
C07D 401/14, 403/12, 417/12

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(21) International Application Number:
PCT/US2003/013605

Declarations under Rule 4.17:

(22) International Filing Date: 1 May 2003 (01.05.2003)

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU,
SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,
UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/377,510 1 May 2002 (01.05.2002) US

(71) Applicant (for all designated States except US): VERTEX
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— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO
patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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(74) Agents: HALEY, James, F. et al.; c/o Fish & Neave, 1251
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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
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(88) Date of publication of the international search report:
5 February 2004

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CRYSTAL STRUCTURE OF AURORA-2 PROTEIN AND BINDING POCKETS THEREOF

(57) Abstract: The present invention provides crystalline molecules or molecular complexes which comprise binding pockets of Aurora-2 or its homologues. The invention also provides crystals comprising Aurora-2. The present invention also relates to a computer comprising a data storage medium encoded with the structural coordinates of Aurora-2 binding pockets and methods of using a computer to evaluate the ability of a compound to bind to the molecule or molecular complex. This invention also provides methods of using the structure coordinates to solve the structure of homologous proteins or protein complexes. In addition, this invention provides methods of using the structure coordinates to screen for and design compounds, including inhibitory compounds, that bind to Aurora-2 or homologues thereof.

WO 2003/092607 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/13605

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 31/517; C07D 401/14, 403/12, 417/12 US CL : 514/266.2, 266.21, 266.23; 544/284 According to International Patent Classification (IPC) or to both national classification and IPC												
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/266.2, 266.21, 266.23; 544/284 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN/CAS, structure search												
C. DOCUMENTS CONSIDERED TO BE RELEVANT												
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
A	WO 02/22602 A2 (VERTEX PHARMACEUTICALS INCORPORATED) 21 March 2002 (21.03.2002), whole document.	1-20, 32-34										
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.												
* Special categories of cited documents: <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"B" earlier application or patent published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"B" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"B" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search		Date of mailing of the international search report										
03 November 2003 (03.11.2003)		28 NOV 2003										
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230		Authorized officer <i>Ellicia D. Roberts</i> for Richard L. Raymond Telephone No. (703) 308-1235										

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/13605

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 21-31
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.



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- ☐ Advanced Keyword Query for: aurora kinase

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- Structure Analysis
- Help

Title STRUCTURE OF HUMAN AURORA-A
122-403 PHOSPHORYLATED ON
THR287, THR288

Authors Bayliss, R., Conti, E.

Primary Citation Bayliss, R., Sardon, T., Vernos, I., Conti, E. Structural Basis of Aurora-A Activation by Tpx2 at the Mitotic Spindle *Molecular Cell* v12 pp.851, 2003

History Deposition 2003-08-06 Release 2003-10-30

Experimental Method Type X-RAY DIFFRACTION Data
[EDS]

Parameters

Resolution [Å]	R-Value	R-Free	Space Group
2.75	0.257 (obs.)	0.296	P 6 ₁ 2 2

Unit Cell

Length [Å]	a	b	c	Angles [°]
81.18	81.18	169.62	alpha 90.00 beta 90.00 gamma 120.00	

Molecular Description Asymmetric Unit monomer (protein 282 residues)
Polymer: 1 Molecule: SERINE/THREONINE KINASE 6
Fragment: CATALYTIC DOMAIN, RESIDUES 122-403 Chains: A; EC No.: 2.7.1.37 Other Details: PHOSPHORYLATED ON THR287, THR288

Functional Class Kinase

Source Polymer: 1 Scientific Name: **Homo sapiens**
system: **Homo sapiens**

Chemical

Component	Identifier Name			Formula	
	TPO	PHOSPHOTHREONINE		$C_4 H_{10} N O_6 P$	
	Mg	MAGNESIUM ION		Mg^{2+}	
	ADP	ADENOSINE-5'-DIPHOSPHATE		$C_{10} H_{15} N_5 O_{10} P_2$	
SCOP Classification (version 1.69)	Domain Info	Class	Fold	Superfamily	F ₂
	d1ol7a_	Alpha and beta proteins (a+b)	Protein kinase-like (PK-like)	Protein kinase-like (PK-like)	Pr kin ca su
CATH Classification (version v2.6.0)	Domain	Class	Architecture	Topology	
	1ol7A1	Mainly Alpha	Orthogonal Bundle	Transfer (Phospho domain)	
	1ol7A2	Alpha Beta	2-Layer Sandwich	Phospho Kinase;	
GO Terms	Polymer		Molecular Function		Biological
	SERINE/THREONINE KINASE 6 (1OL7:A)		<ul style="list-style-type: none"> protein kinase activity protein serine/threonine kinase activity ATP binding 		•


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1MQ4 Im
Bi

- 1MQ4
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- Structural Reports
- Structure Analysis
- Help

Title Crystal Structure of Aurora-A Protein Kinase

Authors Nowakowski, J., Cronin, C.N., McRee, D.E., Knuth, M.W., Nelson, C., Pavletich, N.P., Rodgers, J., Sang, B.-C., Scheibe, D.N., Swanson, R.V., Thompson, D.A.

Primary Citation Nowakowski, J., Cronin, C.N., McRee, D.E., Knuth, M.W., Nelson, C., Pavletich, N.P., Rodgers, J., Sang, B.-C., Scheibe, D.N., Swanson, R.V., Thompson, D.A. Structures of the Cancer-Related Aurora-A, FAK and EphA2 Protein Kinases from Nanovolume Crystallography *Structure* v10 pp.1659-1667, 2002

[Abstract]

History Deposition 2002-09-13 Release 2003-09-16

Experimental Method Type X-RAY DIFFRACTION Data N/A

Parameters

Resolution [Å]	R-Value	R-Free	Space Group
1.90	0.227 (obs.)	0.273	P 6 ₁ 2 2

Unit Cell

Length [Å]	a	b	c	Angles [°]
80.45	80.45	172.17	alpha 90.00	beta 90.00
			gamma 120.00	

Molecular Description Asymmetric Unit monomer (protein 272 residues)
Polymer: 1 Molecule: AURORA-RELATED KINASE 1 Fragment: kinase domain Chains: A; EC No.: 2.7.-.-

Functional Class **Transferase**

Source Polymer: 1 Scientific Name: **Homo sapiens**  (system: **Homo sapiens**)

Related PDB Entries

Id	Details
1MQB	1MQB IS THE CRYSTAL STRU KINASE
1MP8	1MP8 IS the Crystal structure of

Chemical Component

Identifier Name	Formula
PO4 PHOSPHATE ION	$O_4 P^{3-}$
MG MAGNESIUM ION	Mg^{2+}
ADP ADENOSINE-5'-DIPHOSPHATE	$C_{10} H_{15} N_5 O_{10} P_2$

SCOP Classification (version 1.69)

Domain Info	Class	Fold	Superfamily	Fa
d1mq4a_	Alpha and beta proteins (a+b)	Protein kinase-like (PK-like)	Protein kinase-like (PK-like)	Pr kii ca su

CATH Classification (version v2.6.0)

Domain	Class	Architecture	Topolog
1mq4A1	Mainly Alpha	Orthogonal Bundle	Transfe (Phosp domair
1mq4A2	Alpha Beta	2-Layer Sandwich	Phosph Kinase;

GO Terms

Polymer	Molecular Function	Biologi
AURORA-RELATED KINASE 1 (1MQ4:A)	<ul style="list-style-type: none"> protein kinase activity protein serine/threonine kinase activity ATP binding 	•



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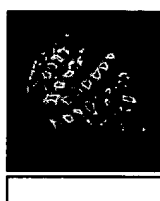
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☒ 2C6D



Characteristics

Classification

Compound

Authors

AURORA A KINASE ACTIVATED MU' (T287D) IN COMPLEX WITH ADPNF

Release Date: 11-Jan-2006 Exp. Method:

Resolution: 2.20 Å

Transferase

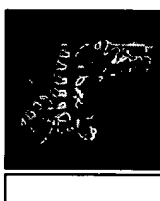
Mol. Id: 1 Molecule: Serine/threonine Prote

Fragment: Catalytic Kinase Domain Residues

Mutation: YES

Heron, N.M., Anderson, M., Blower D.P., Breed, J., Eden, J.M., Green, G.B., Johnson, T., Jung, F.H., Mcm H.H.J., Mortlock, A.A., Pannifer, A. R.A., Pink, J., Roberts, N.J., Rowse

☒ 2C6E



Characteristics

Classification

Compound

Authors

AURORA A KINASE ACTIVATED MU' (T287D) IN COMPLEX WITH A 5-AMINOPYRIMIDINYL QUINAZOLIN INHIBITOR

Release Date: 11-Jan-2006 Exp. Method:

Resolution: 2.10 Å

Transferase/inhibitor Complex

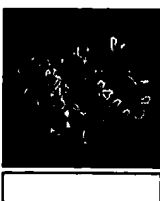
Mol. Id: 1 Molecule: Serine/threonine Prote

Fragment: Catalytic Kinase Domain Residues

Mutation: YES

Heron, N.M., Anderson, M., Blower D.P., Breed, J., Eden, J.M., Green, G.B., Johnson, T., Jung, F.H., Mcm H.H.J., Mortlock, A.A., Pannifer, A. R.A., Pink, J., Roberts, N.J., Rowse

☒ 1OL7



Characteristics

Classification

Compound

Authors

STRUCTURE OF HUMAN AURORA-A 403 PHOSPHORYLATED ON THR287 THR288

Release Date: 30-Oct-2003 Exp. Method:

Resolution: 2.75 Å

Kinase

Mol. Id: 1 Molecule: Serine/threonine Kina:

Fragment: Catalytic Domain Residues 122 40

Bayliss, R., Sardon, T., Vernos, I.,

☒ 1OL5**STRUCTURE OF AURORA-A 122-403 PHOSPHORYLATED ON THR287, TH AND BOUND TO TPX2 1-43****Characteristics**

Release Date: 30-Oct-2003 Exp. Method:

Resolution: 2.50 Å

Classification**Complex(kinase/cell Division Prote**

Mol. Id: 1 Molecule: Serine/threonine Kina:

Compound

Fragment: Catalytic Domain Residues 122 40

Molecule: Restricted Expression Proliferation .

100 Fragment: N Terminal Fragment Residu

Authors

Bayliss, R., Sardon, T., Vernos, I.,

☒ 1OL6**STRUCTURE OF UNPHOSPHORYLAT D274N MUTANT OF AURORA-A****Characteristics**

Release Date: 30-Oct-2003 Exp. Method:

Resolution: 3.00 Å

Classification**Kinase**

Mol. Id: 1 Molecule: Serine/threonine Kina:

Compound

Fragment: Catalytic Domain Residues 122 40

Mutation: YES

Authors

Bayliss, R., Sardon, T., Vernos, I.,

☒ 1MQ4**Crystal Structure of Aurora-A Prote Kinase****Characteristics**

Release Date: 16-Sep-2003 Exp. Method:

Resolution: 1.90 Å

Classification**Transferase****Compound**

Mol. Id: 1 Molecule: Aurora Related Kinase

Fragment: Kinase Domain

Authors

Nowakowski, J., Cronin, C.N., McR D.E., Knuth, M.W., Nelson, C., Pavl N.P., Rodgers, J., Sang, B.-C., Sch D.N., Swanson, R.V., Thompson, D

☒ 1MUO**CRYSTAL STRUCTURE OF AURORA- ONCOGENIC SERINE-THREONINE K****Characteristics**

Release Date: 15-Apr-2003 Exp. Method:

Resolution: 2.90 Å

Classification**Transferase****Compound**

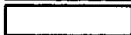
Mol. Id: 1 Molecule: Aurora Related Kinase

Fragment: Aurora 2 Kinase Domain Residues

Authors

Cheetham, G.M.T., Knegt, R.M.A., J.T., Renwick, S.B., Swenson, L., V P., Lippke, J.A., Austen, D.A.

☒ 2F4J**Structure of the Kinase Domain of ; Imatinib-Resistant Abl Mutant in Co with the Aurora Kinase Inhibitor V)**

**Characteristics****Release Date:** 24-Jan-2006 **Exp. Method:****Classification****Resolution:** 1.91 Å**Transferase****Compound****Mol. Id:** 1 **Molecule:** Proto Oncogene Tyros**Abl1** **Fragment:** Kinase Domain Residues 22**Mutation:** H396P**Authors****Young, M.A., Shah, N.P., Chao, L.H M., Milanov, Z.V., Biggs III, W.H., D.K., Patel, H.K., Zarrinkar, P.P., L D.J., Sawyers, C.L., Kuriyan, J.**☒ **1MP8****Characteristics****Crystal structure of Focal Adhesion Kinase (FAK)****Release Date:** 16-Sep-2003 **Exp. Method:****Classification****Resolution:** 1.60 Å**Transferase****Compound****Mol. Id:** 1 **Molecule:** Focal Adhesion Kinase**Fragment:** Kinase Domain**Authors****Nowakowski, J., Cronin, C.N., McR D.E., Knuth, M.W., Nelson, C.G., P; N.P., Rodgers, J., Sang, B.-C., Sch; D.N., Swanson, R.V., Thompson, D**☒ **2BFX****Characteristics****MECHANISM OF AURORA-B ACTIVATION BY INCENP AND INHIBITION BY HESPERIDIN.****Release Date:** 03-May-2005 **Exp. Method:****Classification****Resolution:** 1.80 Å**Transferase Complex****Compound****Mol. Id:** 1 **Molecule:** Loc398457 Protein**Fragment:** Catalytic Domain Residues 78 361**Molecule:** XI Incenp **Fragment:** N Terminal Residues 798 840**Authors****Sessa, F., Mapelli, M., Ciferri, C., T C., Areces, L.B., Schneider, T.R., S P.T., Musacchio, A.**

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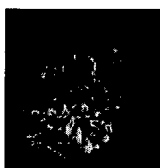
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☒ **2BFY**



Characteristics

Classification

Compound

Authors

COMPLEX OF AURORA-B WITH INCENP AND HESPERIDIN.

Release Date: 03-May-2005 Exp. Method:

Resolution: 1.80 Å

Transferase Complex

Mol. Id: 1 Molecule: Loc398457 Protein

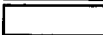
Fragment: Catalytic Domain Residues 78 361

Mol. Id: 2 Molecule: XI Incenp Fragment

Fragment Residues 798 840

Sessa, F., Mapelli, M., Ciferri, C., T. C., Areces, L.B., Schneider, T.R., S. P.T., Musacchio, A.

☒ **2BMC**



Characteristics

Classification

Compound

Authors

AURORA-2 T287D T288D COMPLEX WITH PHA-680632

Release Date: 17-Mar-2005 Exp. Method:

Resolution: 2.60 Å

Transferase

Mol. Id: 1 Molecule: Serine Threonine Proti

Fragment: Catalytic Domain Residues 100 40

Mutation: YES

Fancelli, D., Berta, D., Bindi, S., Ca A.D., Catana, C., Forte, B., Giordar P., Mantegani, S., Meroni, M., Moll V., Severino, D., Storici, P., Tonani M., Vulpetti, A., Vianello, P., Izzo, A., Rusconi, L.

☒ **1MQB**



Characteristics

Classification

Compound

Authors

Crystal Structure of Ephrin A2 (ephrin Receptor Protein Kinase)

Release Date: 16-Sep-2003 Exp. Method:

Resolution: 2.30 Å

Transferase

Mol. Id: 1 Molecule: Ephrin Type a Recepto

Fragment: Kinase Domain

Nowakowski, J., Cronin, C.N., McR D.E., Knuth, M.W., Nelson, C., Pavl N., Rogers, J., Sang, B.C., Scheibe,

D.N., Swanson, R.V., Thompson, D.A.

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(11) **EP 1 522 580 A1**

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
13.04.2005 Bulletin 2005/15

(51) Int Cl.7: **C12N 9/12, C07K 14/47,**
C07D 209/42

(21) Application number: **03023136.9**

(22) Date of filing: **10.10.2003**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

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Remarks:

The sequence listing, which is published as annex to the application documents, was filed after the date of filing. The applicant has declared that it does not include matter which goes beyond the content of the application as filed.

(54) **Crystals of an aurora-a tpx2 complex, tpx2 binding site of aurora-a, aurora-a ligands and their use**

(57) The present invention relates to crystals of phosphorylated Aurora-A kinase fragment alone and in complex with a ligand, amino acid residues 1-43 of human TPX2. This invention also relates to methods for designing and selecting ligands, in particular allosteric inhibitors of Aurora-A, that bind to the Aurora-A kinase and their use. Further, the present invention relates to certain indene and indole derivatives. The present in-

vention relates to crystals of phosphorylated Aurora-A kinase alone and in complex with a ligand, amino acid residues 1-43 of human TPX2. This invention also relates to methods for designing and selecting ligands that bind to the Aurora-A kinase and their use. Further, the present invention relates to certain indene and indole derivatives.

EP 1 522 580 A1



European Patent
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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 03 02 3136 shall be considered, for the purposes of subsequent proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 03/031606 A (PANNIFER ANDREW DAVID BRUCE ; PAUPTIT RICHARD ALEXANDER (GB); ROWSE) 17 April 2003 (2003-04-17) * the whole document *	5,9	C12N9/12 C07K14/47 C07D209/42
D,X	EYERS PATRICK A ET AL: "A novel mechanism for activation of the protein kinase Aurora A." CURRENT BIOLOGY, vol. 13, no. 8, 15 April 2003 (2003-04-15), pages 691-697, XP002275012 ISSN: 0960-9822 (ISSN print) * the whole document *	5	
Y	* the whole document *	1-4	
X	KUFER THOMAS A ET AL: "Human TPX2 is required for targeting Aurora-A kinase to the spindle" JOURNAL OF CELL BIOLOGY, vol. 158, no. 4, 19 August 2002 (2002-08-19), pages 617-623, XP002275013 ISSN: 0021-9525 * the whole document *	5	
Y	* the whole document *	1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C12N C07K C07D
INCOMPLETE SEARCH <p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search Munich		Date of completion of the search 25 March 2004	Examiner Schwachtgen, J-L
CATEGORY OF CITED DOCUMENTS <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

1
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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 03 02 3136

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	MUELLER U ET AL: "Development of a technology for automation and miniaturization of protein crystallization" BRAUWELT, NUERNBERG, DE, vol. 85, no. 1, 23 January 2001 (2001-01-23), pages 7-14, XP004315104 ISSN: 0168-1656 * the whole document *	1-4	
T	BAYLISS RICHARD ET AL: "Structural basis of Aurora-A activation by TPX2 at the mitotic spindle." MOLECULAR CELL, vol. 12, no. 4, October 2003 (2003-10), pages 851-862, XP002275014 ISSN: 1097-2765 (ISSN print)		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	WO 94/03427 A (WARNER LAMBERT CO) 17 February 1994 (1994-02-17) * the whole document *		



European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 03 02 3136

Claim(s) not searched:
6-8

Reason for the limitation of the search (non-patentable invention(s)):

Article 52 (2)(d) EPC - Presentation of information

Further limitation of the search

Claim(s) not searched:
10-12, 24-26

Reason for the limitation of the search:

Claims 10-12 and 24 (in part) relate to compounds defined as modulators or allosteric inhibitors, which bind to any of a number of residues of Aurora-A. The claims cover all such compounds, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC no such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC) as an attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search impossible.

The same objection applies to claims 25 and 26, insofar as they relate to uses of the compounds according to claims 10-12.



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Application Number

EP 03 02 3136

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
- 1-5, 9



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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 03 02 3136

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-5, 9

A crystal of phosphorylated Aurora-A kinase complexed with
human TPX2

2. claims: 13-26

Indole and indene derivatives and their uses

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 03 02 3136

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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25-03-2004

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03031606	A	17-04-2003	WO	03031606 A2	17-04-2003
WO 9403427	A	17-02-1994	AU	672224 B2	26-09-1996
			AU	4799493 A	03-03-1994
			CA	2140440 A1	17-02-1994
			CZ	9500288 A3	12-06-1996
			EP	0654024 A1	24-05-1995
			HU	71553 A2	28-12-1995
			JP	8503450 T	16-04-1996
			RU	2155187 C2	27-08-2000
			SK	13595 A3	13-09-1995
			WO	9403427 A1	17-02-1994
			US	5464861 A	07-11-1995
			US	5556874 A	17-09-1996

EPO FORM P0459

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☐ 1: aurora kinase [Substance Name]

Lir

highly conserved in eukaryotes and involved in many processes during cell division; Aurora A regulates centrosome function during M phase; Aurora-B plays roles in spindle dynamics, chromosome condensation, and cytokinesis

Date introduced: May 18, 1995

Registry Number: EC 2.7.1.-

Heading Mapped to:

- [Protein-Serine-Threonine Kinases](#)

Entry Terms:

- aur kinase
- aurora kinase A
- Aik protein
- AURORA2 protein
- Breast-tumor-amplified kinase
- BTAK protein
- serine/threonine protein kinase 15
- STK15 kinase
- aurora kinase B
- AIK2 protein
- aurora-related kinase 2
- aurora1 protein
- serine/threonine protein kinase 12
- STK12 protein
- aurora kinase C
- AIK3 protein
- Aurora/Ipl1-related kinase 3
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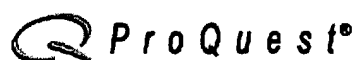
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